Gene Section

MCAM (melanoma cell adhesion molecule)

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Identity

Other names: CD146, METCAM, MUC18, Gicerin
HGNC (Hugo): MCAM
Location: 11q23.3

DNA/RNA

Description

Human METCAM (huMETCAM), a CAM in the immunoglobulin-like gene superfamily, is an integral membrane glycoprotein. Alternative names for METCAM are MUC18 (Lehmann et al., 1987), CD146 (Anfosso et al., 2001), MCAM (Xie et al., 1997), MeICAM (Shih et al., 1994a), A32 (Shih et al., 1994b), and S-endo 1 (Bardin et al., 1996).
To avoid confusion with mucins and to reflect its biological functions, we have renamed MUC18 as METCAM (metastasis CAM), which means an immunoglobulin-like CAM that affects or regulates metastasis, (Wu, 2005). METCAM/MUC18 gene is located on human chromosome 11q23.3.

Transcription

The major transcript of the gene in most human epithelial cancer cell lines is about 3.3 kb (Wu et al., 2001a).
A distinct short form resulting from alternative splicing of the gene of gicerin, the chicken homolog of METCAM, has been found (Taira et al., 1995). Though the expression of a short form of METCAM has been briefly mentioned in human melanoma cells (Lehmann et al., 1987), its function is not known since it is expressed at a much lower level than the major form in various cancer cell lines (Wu, unpublished observation). Interestingly, a truncated form with a deletion in some portion of the cytoplasmic domain has been found in a prostate cancer specimen X9479, a cell line derived from specimens of nasopharyngeal carcinomas and other cancers (Wu, unpublished observations). Further systematic search for the function of this minor form should be carried out.

Pseudogene

METCAM/MUC18 may not have a pseudogene.

Protein

Note

Human METCAM/MUC18 cDNA encodes 646 amino acids, about 115-150 kDa protein.

Description

The huMETCAM has 646 amino acids that include a N-terminal extra-cellular domain of 558 amino acids, which has 28 amino acids characteristics of a signal peptide sequence at its N-terminus, a transmembrane domain of 24 amino acids (amino acids 559-583), and a cytoplasmic domain of 64 amino acids at the C-terminus. HuMETCAM has eight putative N-glycosylation sites (Asn-X-Ser/Thr), of which six are conserved, and are heavily glycosylated and sialylated resulting in an apparent molecular weight of 113000-150000. The extra-cellular domain of the protein comprises five immunoglobulin-like domains (V-V-C2-C2-C2) (Lehmann et al., 1987; Wu et al., 2001a; Wu, 2005) and an X domain (Wu et al., 2001a; Wu, 2005).
HuMETCAM protein structure. SP stands for signal peptide sequence, V1, V2, C2, C2’, C2’’ for five Ig-like domains (each held by a disulfide bond) and X for one domain (without any disulfide bond) in the extracellular region, and TM for transmembrane domain. P stands for five potential phosphorylation sites (one for PKA, three for PKC, and one for CK2) in the cytoplasmic tail. The six conserved N-glycosylation sites are shown as wiggled lines in the extracellular domains of V1, between C2’ and C2’’, C2’’, and X.

The cytoplasmic tail contains peptide sequences that will potentially be phosphorylated by protein kinase A (PKA), protein kinase C (PKC), and casein kinase 2 (CK 2) (Lehmann et al., 1987; Wu et al., 2001a; Wu, 2005). My lab has also cloned and sequenced the mouse METCAM (moMETCAM) cDNA, which contains 648 amino acids with a 76.2% identity with huMETCAM, suggesting that moMETCAM is likely to have biochemical properties and biological functions similar to the human counterpart (Yang et al., 2001; Wu, 2005).

The structure of the huMETCAM protein is depicted in figure above, suggesting that METCAM, similar to most CAMs, plays an active role in mediating cell-cell and cell-extracellular interactions, crosstalk with many intracellular signaling pathways, and modulating the social behaviors of cells (Cavallaro and Christofori, 2004; Wu, 2005). Recent work supports an emerging novel function of METCAM in tumor angiogenesis and perhaps it plays an important role in the metastasis of tumor cells (Wu, 2010; Wu, 2012).

Function

Similar to other cell adhesion molecules (CAMs), METCAM/MUC18 does not merely act as a molecular glue to hold together homotypic cells in a specific tissue or to facilitate interactions of heterotypic cells; It also actively governs the social behaviors of cells by affecting the adhesion status of cells and modulating cell signaling (Cavallaro and Christofori, 2004).

It controls cell motility and invasiveness by mediating the remodeling of cytoskeleton (Cavallaro and Christofori, 2004). It also actively mediates the cell-to-cell and cell-to-extracellular matrix interactions to allow cells to constantly respond to physiological fluctuations and to alter/repair the surrounding microenvironment for survival (Chambers et al., 2002).

It does so by crosstalk with cellular surface growth factor receptors, which interact with growth factors that may be secreted from stromal cells or released from circulation and embedded in the extracellular matrix (Chambers et al., 2002; Cavallaro and Christofori, 2004).

Thus an altered expression of METCAM/MUC18 affects the motility and invasiveness of many epithelial tumor cells in vitro and metastasis in vivo (Chambers et al., 2002; Cavallaro and Christofori, 2004; Wu, 2005). METCAM/MUC18 may also play an important role in the favorable soil that provides a proper microenvironment at a suitable period to awaken the dormant metastatic tumor cells to enter into an aggressive growth phase.

Evidence have been documented that aberrant expression of huMETCAM/MUC18 actually affects the motility and invasiveness of many tumor cells in vitro and metastasis in vivo.

Thus HuMETCAM/MUC18 plays an important role in promoting the malignant progression of many cancer types (Cavallaro and Christofori, 2004; Wu, 2005).
**Homology**

Human METCAM/MUC18 protein shares high homology with the mouse METCAM/MUC18 (Wu et al., 2001a; Yang et al., 2001) and other Ig-like CAMs, especially the NCAMs (Lehmann et al., 1987).

**Mutations**

Note
Several point mutations have been found in huMETCAM/MUC18 protein from human cancers (Wu et al., 2001a).

**Implicated in**

**Various cancers**

Note
The protein is overly expressed in most (67%) malignant melanoma cells (Lehmann et al., 1987); and in most (more than 80%) pre-malignant prostate epithelial cells (PIN), high-grade prostatic carcinoma cells, and metastatic lesions (Wu et al., 2001b; Wu, 2004). HuMETCAM is also expressed in other cancers, such as gestational trophoblastic tumors, leiomyosarcoma, angiosarcoma, haemangiomia, Kaposi's sarcoma, schwannoma, some lung squamous and small cell carcinomas, some breast cancer, some neuroblastoma (Shih, 1999), and also nasopharyngeal carcinoma (Lin et al., 2012) and ovarian cancer (Wu et al., 2012).

**Breast cancer**

Note
Over-expression of huMETCAM has been shown to promote tumorigenesis of four breast cancer cell lines in athymic nude mice and perhaps the malignant progression of breast cancer cells (Zeng et al., 2011; Zeng et al., 2012).

**Prognosis**
Over-expression of huMETCAM/MUC18 has been implicated in a poor prognosis of breast cancer.

**Prostate cancer**

Note
Over-expression of huMETCAM has been shown to promote tumorigenesis and metastasis of human prostate cancer LNCaP cells in athymic nude mice (Wu et al., 2001a; Wu et al., 2001b; Wu, 2004; Wu et al., 2004; Wu et al., 2011).

**Disease**
Human prostate cancer (Wu et al., 2001a; Wu et al., 2001b; Wu, 2004; Wu et al., 2004; Wu et al., 2011) and the TRAMP models (Wu et al., 2005).

**Prognosis**
Over-expression of huMETCAM/MUC18 has been implicated in a poor prognosis of prostate cancer (Wu et al., 2001a; Wu et al., 2001b, Wu, 2004).

**Oncogenesis**
METCAM/MUC18 promotes the oncogenesis of human prostate cancer cells (Wu et al., 2001a; Wu et al., 2001b; Wu, 2004; Wu et al., 2004; Wu et al., 2011).

**Melanoma**

Note
Over-expression of huMETCAM has been shown to promote metastasis, but not the tumorigenesis, of human melanoma (Xie et al., 1997; Schlagbauer-Wadl et al., 1999) and mouse melanoma cells (Yang et al., 2001; Wu et al., 2008) in immunodeficient nude mice.

**Prognosis**
Over-expression of huMETCAM/MUC18 has been implicated in a poor prognosis of melanoma (Lehmann et al., 1987; Shih, 1999).

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